BLA 99-2672
CLINICAL REVIEW

1.0 GENERAL INFORMATION

Applicant:	Hoffman LaRoche	
Product:	Generic:	Pegylated Interferon alfa-2a
	Trade:	PEGASYS™
Route:	Subcutaneous	
Indication:	Treatment of chronic hepatitis C virus infection	
Related INDs:	[	
		]
Related BLAs:	BLA 99-14888 (Schering-Plough Pegylated Interferon alfa-2b)	
Milestone Dates:	Date of Original BLA filing: May 19, 2000	

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2.0 SUMMARY

The sponsor has developed a pegylated form of their interferon alfa-2a product. After non-clinical pharmacology and toxicology assessment, Phase 1 and Phase 2 studies were performed to establish preliminary safety, pharmacokinetic and dose ranging efficacy assessment in the clinical indication evaluated. The applicant is seeking the indication of treatment of patients with chronic hepatitis C (CHC) infection.

Three pivotal clinical trials were performed – one in CHC patients with compensatory cirrhosis or transition to cirrhosis and two in CHC patients without cirrhosis but with liver histology consistent with CHC infection. One of the non-cirrhosis trials was performed entirely outside the United States, but the other two studies had significant participation from U.S. clinical centers and enrolled significant numbers of United States citizens.

In the three pivotal trials, patients were well distributed for baseline prognostic variables and appropriate efforts were made to obtain follow-up safety and efficacy data on all patients. The objectives, endpoints and data collection methods were well standardized across studies and allowed results to be integrated for both efficacy and safety assessments.

PEG-IFN at doses of 90, 135 or 180 mcg per week subcutaneous x 48 weeks was compared to control arms of standard interferon alfa-2a therapy at either a 3 MIU thrice weekly subcutaneous dose or an induction regimen of standard IFN (6MIU tiw x 12 weeks, then 3 MIU tiw x 36 weeks). The primary efficacy outcome measure was sustained virologic and biochemical response 24 weeks after the completion of the 48 weeks of treatment. Virologic response was measured as the absence of detectable HCV by a ---------- test and biochemical response was measured as a normalization of ALT levels compared to baseline elevated levels. Secondary efficacy variables included end-of-treatment virologic response, histologic response and quality of life assessment. Safety was monitored by assessment and recording of emerging adverse events, as well as several laboratory measurements of organ function. Antibody formation to either IFN or PEG-IFN was also assessed.

In each of the three pivotal studies PEG-IFN proved superior to IFN in causing a sustained virologic and biochemical response. Responses were better in genotype non-1 versus 1, and in patients with low viral load compared to high.

The spectrum of adverse events subsequent to the start of PEG-IFN therapy was generally the same as observed in the IFN control groups. However, PEG-IFN caused worse neutropenia and thrombocytopenia than IFN and there were indications that these differences resulted in greater infectious complications during and after treatment. In addition, there appeared to be an unusual number of deaths in the PEG-IFN groups due to opiate overdose. It was not clear whether a causative relationship existed between the use of PEG-IFN and opiate abuse/overdose behavior, but this observation is not

inconsistent with literature that suggests a role for IFN in modulating CNS opiate pathways and the possible role of these pathways in the neurobiology of addictive behavior.

3.0 BACKGROUND

3.1 Natural History and Treatment of Hepatitis C

The Hepatitis C virus is a linear, single-stranded, 9500-nucleotide RNA virus that constitutes its own genus in the family Flaviviridae. Epidemiological studies have shown that HCV is mostly transmitted via the percutaneous (needle sharing, blood transfusions, etc.) route, with significantly less cases from perinatal or sexual transmission origins. Regardless of the epidemiological mode of transmission of HCV, chronic hepatitis C (CHC) follows acute hepatitis C in 50-70% of cases. An estimated 2.7 million Americans suffer from CHC infection. Since CHC can be expected to result in progressive fibrotic and cirrhotic changes in liver histology and function over time, it is imperative that effective therapies be developed to eradicate the virus in these patients.

At this time, interferon alfa 2a and 2b (IFN), pegylated interferon alfa 2a, interferon alfa 2b + ribavirin, and pegylated interferon alfa 2a + ribavirin therapies have been developed and approved by FDA for the treatment of CHC. Interferon exerts its effect on HCV through antiviral and immunomodulatory mechanisms. Several interferon products are marketed and all have the same general efficacy and safety profile. Sustained viral response (reduction of virus to undetectable levels for sustained periods after treatment completion) rates to IFN therapy occur in approximately 10-20% of patients treated. Prognostic factors for treatment response include initial HCV genotype and initial HCV viral load. The addition of ribavirin to IFN alfa 2b therapy has resulted in an increase in sustained viral response rates to approximately 40 - 45% in the populations chosen for study.

Subcutaneous injection of IFN results in pharmacological concentrations that begin to wane within hours (half-life of approximately 8 hours). Since the viral response to IFN has been shown to wane in relation to serum concentrations of IFN, it was proposed that modifying the formulation of IFN to cause longer, sustained concentrations might improve the efficacy of the agent. A pegylated version of IFN alfa 2b was developed and approved by FDA in 2000. Sustained viral response for this product was approximately 25%. Subsequently, this product was combined with ribavirin, and the combination produced a modest improvement in SVR compared to IFN + Ribavirin control (52 vs. 46% SVR, respectively).

The product under review in this BLA is a pegylated version of interferon alfa-2a (PEG-IFN). The sponsor completed a clinical development plan to assess the efficacy and safety of PEG-IFN in patients with chronic hepatitis C infection.

3.2 Regulatory History

Early Clinical Development

The sponsor performed a series of Phase 1 studies in normal volunteers and performed pharmacokinetic analyses of the product in patients with HCV infection and who were enrolled into Phase 2 and 3 clinical trials. Please see the Clinical Pharmacology review for details of findings.

The sponsor performed a Phase 2 Dose-Ranging Study testing the safety and efficacy of the product at doses of 45, 90, 180, and 270 mcg per week for 48 weeks. Patients had hepatitis C disease without cirrhosis. Details of the study and results will not be presented in this document* but were the basis of discussions with the Agency to plan for pivotal studies with the product.

The results of the Phase 2 dose-ranging study supported the use of the 180 mcg dose as the high dose and 90 mcg as the low dose in the Phase 2/3 and Phase 3 program.

> * with the exception of discussion of a death due to opiate overdose and other serious adverse events that occurred in this study.

4.0 PIVOTAL STUDIES

Overview of Pivotal Studies

In an effort to allow comparability of results between studies, the sponsor designed the pivotal studies with very similar objectives, entry criteria and outcome measures. When amendments were made to critical elements of the studies, they tended to be applied to all three pivotal studies.

An important distinction between the first Phase 2/3 trial (NV15495) and the next two Phase 3 trials (NV15496 and 15497) was the degree to which patients with cirrhosis were entered into the study. The NV15495 trial specifically sought to determine the safety and efficacy of PEG-Interferon alfa 2-a in patients with compensated cirrhosis. In the case of studies NV15496 and NV15497, the emphasis was on patients without cirrhosis. Cirrhotic patients were not specifically excluded, but they made up a small minority of the patients in the study (20%).

As will be described, there was little fundamental difference observed regarding the safety or efficacy of PEG-IFN in non-cirrhotic versus cirrhotic patients.

4.1 Clinical Trial NV15495

Title A Phase II, Open-Label, Randomized, Multicenter, Parallel Dose Study

Evaluating the Safety and Efficacy of PEG-IFN vs. Roferon in the Treatment of Patients with Chronic Hepatitis C with Cirrhosis

4.1.1 Objectives and Design

This Phase 2/3 was to be performed at 20-25 centers in the U.S., Canada and U.K. By the end of the study, the trial had been expanded to 30 centers. The objectives were to compare the safety/tolerability and efficacy of 90 and 180 mcg of PEG administered subcutaneously and weekly to Roferon administered t.i.w. over a 48 week treatment period followed by a 24 week untreated follow-up period in patients with chronic hepatitis C complicated by compensated liver cirrhosis or transition to cirrhosis. The study was also designed to study the pharmacokinetic profile of PEG-IFN in this patient population.

The statistical design was that of an open-label, randomized, parallel group study. Treatment groups and numbers of patients were to be as follows:

N=80	Roferon 3 MIU tiw
N=80	PEG 90 mcg qw
N=80	PEG 180 mcg qw

By the end of the study, 271 patients had been randomized. Randomization was 1:1:1, with stratification by center.

4.1.2 Inclusion/Exclusion Criteria

Inclusion Criteria: Men and women ≥ 18 years old; serologically proven CHC (anti-HCV antibody test) with compensated liver disease (Child-Pugh Grade A as determined by biopsy within 12 months prior to first dose of study drug)-and with cirrhosis or transition to cirrhosis; elevated serum ALT as determined by two abnormal values taken ≥ 14 days apart during the six months before the first dose of study drug with at least one of the determinations obtained ≤ 35 days prior to first dose; quantifiable HCV RNA by ----

Exclusion Criteria: Other forms of liver disease, HIV and hepatocellular carcinoma, pre existing severe depression, cardiac, renal or seizure disorder, retinopathy and prior IFN treatment

4.1.3 Endpoints

- Efficacy:

The primary efficacy endpoint was Sustained Response defined as normalized serum ALT concentration and undetectable HCV RNA by ---------- at the end of 24 weeks of follow-up.

Secondary efficacy endpoints were: End of treatment virologic and biochemical response; Sustained response (virologic response) at 24 weeks following completion of

treatment compared to pre-treatment rates; Histological improvement as measured by comparison of findings pre-treatment and at the end of the 24 weeks of untreated f/u (biopsy within 14 days of EOT). Quality of Life and Fatigue Severity Scale Questionnaire assessment

- Safety:

Safety monitoring consisted of assessment of vital signs, labs, adverse events, ECG and chest X-ray. Safety monitoring consisted of assessment of vital signs, labs, adverse events, ECG and chest X-ray. The trial had a Safety Review Board that was to meet every 2-3 months. Safety labs were drawn at various timepoints during treatment and at follow-up and consisted of testing for hematology (CBC with differential, platelets), biochemistry (alkaline phosphatase, AST, ALT, total bilirubin, total protein, albumin, BUN, serum creatinine, chloride, potassium, sodium, calcium, phosphate, uric acid, and cholesterol and triglyceride), urinalysis and thyroid function. Assessment for IFN antibodies was performed at baseline and Week 56.

4.1.4 Statistical Considerations

The statistical analytical plan was based on the goal of demonstrating that the efficacy of either PEG-IFN dose arms was superior to that of the standard IFN control group.

4.1.4.1 Sample Size:

The sample size was predicated on the assumption that the combined sustained response in terms of both virological and biochemical response at the end of untreated follow up of Roferon in cirrhotic patients from historic data was below 5%. 81 patients per treatment arm were required in order to detect a rate of 25% in a PEG treatment arm versus a rate of 5% in the Roferon arm, with a power of 80%, at a two-side significance level of 0.025, adjusting for a dropout rate of 15%. Since a total of two pairwise comparisons (PEG 90 vs. Roferon and PEG 180 vs. Roferon) was made, a significance level of 0.025 was to be used in all statistical testing.

4.1.4.2 Analytical groups:

- The Intent-to-Treat group was all randomized patients.

- A subgroup of the ITT group was referred to as the Standard Treatment group and had the following criteria for exclusion of ITT data from analysis:

--Patients who never took any study medication
--Patients who took less than 25% of the injections (Patients randomized to the PEG arms and took less than 12 injections [36 for Roferon]will be excluded)
--Patients randomized to the PEG who took less than 4 injections at that dose (<12 for Roferon)
--Patients without compensated liver disease of Child-Pugh Grade A classification

--Patients with baseline HCV RNA < 2000 copies/ml
--Patients without two abnormal ALT levels ≥14 days apart during the six months before the first dose of study medication with at least one of the determinations obtained ≤35 days prior to the first dose
--Patients who received previous treatment with IFN
--Patients who received previous treatment with any other systemic antiviral therapy or investigational drug ≤ 3 months prior to the first dose of study medication, unless permitted by the protocol
--Patients with no post-baseline ALT and HCV RNA assessment

Reviewer Comment:

Note that although analyses using the Standard treatment group were performed, the results did not add appreciably to efficacy information about the product. Subgroup analyses of this sort are typically of limited value since bias could be introduced and distribution across treatment groups could be unequal. These results were not requested to be part of the label by the sponsor and they will not be included in this review.

- Primary Efficacy Group – Case Definition of Sustained Responder

For purposes of statistical analyses, the sponsor defined precise case definitions for the primary outcome measure (SVR and SBR at 24 weeks after EOT). Patients without week 68 or 72 data were considered non-responders. Sustained viral responder was defined as having a non-detectable HCV-RNA at both week 68 and week 72. Allowable ranges for collection of these samples were days 464 to 491 for Week 68 and days 492 to 519 for Week 72. Sustained biochemical responder was defined as having a normalized ALT at both week 68 and week 72. Allowable ranges for collection of these samples were days 464 to 491 for Week 68 and days 492 to 519 for Week 72.

In a late amendment to the IND, the [

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Reviewer Comment:

The Agency considered this post-hoc approach to be inherently prone to conscious and/or unconscious bias and decided that use of the original protocol definition of responder represented the least bias approach in determining responder classification. Appendix 1 includes a more thorough review of this issue.

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- Secondary Efficacy Analyses

Secondary Efficacy parameters measured were: Sustained biochemical response rate, induction virological response rate, induction biochemical response rate, end-of-treatment virological response rate, end-of-treatment biochemical response rate, end-of-week 12 virological response rate, end-of-week-12 biochemical response rate, maintenance of virological response after end of treatment, maintenance of biochemical response after end of treatment, absolute and % change from baseline HCV-RNA copies, absolute and % change from baseline ALT levels, duration of virologic response during 48 week treatment period, duration of biochemical response during 48 week treatment period, time to relapse of virologic response, time to relapse of a biochemical response, and histology of liver biopsy and quality of life as measured by the SF-36 scale and the Fatigue Severity Scale (FSS).

- Interim Analyses

An Interim Analysis, to be administrative in intent, was planned during first quarter of 1998, when about half of the patients had completed 4 weeks of treatment. The results of the 4-week virological response and biochemical response were to be used to plan a new study. Another, formal, interim analysis was planned when all patients had completed 16 weeks of treatment. Since the study was not to be terminated even if significantly superior induction response rates were observed in either PEG arm when compared to the IFN arm, no adjustment of significance level was required at the final comparison of sustained response rates.

- Subgroup analyses

The following groups were segregated and analyzed for the primary efficacy endpoint and key secondary efficacy endpoints: Age, gender, BSA, baseline ALT quotient, baseline HCV RNA titers and HCV genotype.

- Safety analysis (Safety Population)

The population for the safety analysis was patients who receive at least one dose of study medication and have at least one post-baseline safety assessment

- Statistical handling of variables

Treatment difference – estimated using least square means and corresponding 95% CI

Time to event variables – used survival analysis techniques including Kaplan-Meier plots, logrank test, Cox

proportional hazards regression model stratified by center. Hazard ratios and corresponding 95% CI were given

Categorical variables – used the Mantel-Haenszel test stratified by center. Odds ratio and corresponding 95% CI were given.

Changes from baseline variables – used analysis of covariance

Incidence of adverse events and lab abnormalities were summarized by treatment group

4.1.5 Results

4.1.5.1 NV15495 Disposition of patients / Distribution of baseline variables

	Stnd IFN	90 PEG	180 PEG
DISPOSITION			
Randomized patients	88	96	87
Rand'd, received drug (SAFETY POP)	86	96	87
Completed treatment	64	78	67
Completed Rx,Completed f/u	58	70	65
Follow-up "compliance"	91%	90%	97%
BASELINE CHARACTERISTICS			
ALT, mean	104.1	104.1	123.3
HCV RNA, mean (10^3 copies/mL)	6309	6308	5663
HAI score, mean	12.8	12.7	13.4
Cirrhosis	76%	79%	79%
Transition to cirrhosis	24%	20%	21%
Noncirrhosis	N/A	1	N/A
Genotype 1a	32%	28%	38%
Genotype 1b	22%	32%	17%

Reviewer Comment:

Baseline variables generally appear evenly distributed amongst the treatment groups. Compliance with the protocol was adequate. The ALT mean is slightly elevated and the HCV mean is slightly lower in the 180 mcg group relative to the other groups. The effect of the primary outcome would be minimal since these two variables have opposite prognostic effects and each would thus likely cancel the other's effect on outcome.

4.1.5.2 Efficacy results

4.1.5.2.1 NV15495 Viral and Biochemical Results

Primary Efficacy Parameter: Sustained Viral Response(SVR) + Sustained Biochemical Response (SBR) (Intent-to-Treat results using the original protocol definition of sustained responder)

Secondary Efficacy Parameters: Sustained Viral Response, Sustained Biochemical Response (Intent-to-Treat results using the original protocol definition of sustained responder)

Group	N	SVR + SBR (ITT) n (%)	SVR (ITT) n (%)	SBR (ITT) n (%)
Stnd Roferon	88	3 (3)	4 (5)	6 (7)
90 PEG	96	11 (11)	12 (13)	14 (15)
180 PEG	87	17 (20)	24 (28)	20 (23)

Reviewer Comment:

There appears to be a dose-response effect in the ability of pegylated interferon alfa-2a to induce a sustained viral response.

4.1.5.2.2 NV15495 Liver Biopsy Results

All Patients	Stnd IFN	90 PEG	180 PEG
	n=88	n=96	n=87
Number with response	n=17	n=27	n=37
% with improvement (>2 decrease)	19	28	43
Patients With Paired Biopsies	n=55	n=61	n=68
Number with response	n=17	n=27	n=37
Pre-treatment HAI, mean	12.7	12.6	13.4
Histologic activity index, mean change*	-0.8	-1.2	-2.6
% with improvement (>2 decrease)	31	44	54

Reviewer's Comment:

Percent of paired biopsies for the standard IFN, and the 90 and 180 mcg PEG-IFN, represent only 63, 64 and 78%, respectively, of the total number of patients in each treatment group. Inferring any conclusions about the effect of treatment on histology in the presence of such a large amount of missing data is problematic.

4.1.5.2.3 NV15495 Quality of Life Results

	Stnd. IFN	**PEG 90**	**PEG 180**
Quality of Life - SF36 (change in mean from baseline)			
Mental health index (decrease=worse)	-1.6	-1.5	-3.7
Standardized mental component	-0.7	-1	-2.8
At week 72: Much + somewhat better than 1 yr ago?	26%	26%	48%
Quality of Life - Fatigue Severity Scale			
Total FSS (sum # 1-9, mean change) (week72 vs. baseline) (increase=feels worse)	1.2	1.9	2.5

Reviewer Comment:

The results from assessment of quality of life appear inconsistent. Two of the three scales indicate a dose-response worsening for mental health and fatigue scores. One of the three scores (global assessment) indicates an improvement, but without a dose-related effect. Taken together, the results indicate either no effect or a worsening effect on quality of life as the result of pegylated interferon use. The scoring systems that were used have not yet been validated as a tool to measure the effect of interferon products on quality of life, so this might have contributed to the equivocal results. Also, use of a subjective endpoint such as Quality of Life in an open label clinical trial such as this might have biased the results and therefore disallow any conclusions.

4.1.5.2.4 NV15495 Subgroup Analysis

	Stnd IFN	90 PEG	180 PEG
Viral Sustained Response (all patients)	5%	13%	28%
Viral Sustained Response (subgroups, %)			
Age < 40	0	5	23
Age > 40	5	14	29
Male	5	11	27
Female	4	16	29
Caucasian	4	11	31
Non-caucasian	9	22	8
ALT Quo <3	0	13	25
ALT Quo > 3	10	11	29
RNA < 2 mil	5	18	35
RNA > 2 mil	4	8	20
Geno 1a	0	4	9
Geno 1b	0	6	13
Geno non-1	10	25	50
HAI <10	0	0	40 (2/5)
HAI >10	5	14	27
Histo cirrhosis	4	13	29
Histo non-cirrhosis	0	0	0
Histo transition to cirrhosis	5	11	22%

Reviewer Comment:

Regarding the efficacy in the subgroup of "Non-Caucasian", the accuracy of this number is questionable because of the small sampling (n= 11, 9 and 12 for standard IFN, 90 PEG and 180 PEG, respectively). The higher response rates for initial RNA <2 million and for genotype non-1 are consistent with previous IFN trials showing superior results in these patient groups.

4.1.5.3 Safety results

The following table describes the extent and reasons for either withdrawal from study or dose modification in study NV15495.

4.1.5.3.1 NV15495 Withdrawals and Dose Modifications

	Stnd IFN	90 PEG	180 PEG
Withdrawals total	24 (27%)	18 (19%)	20 (23%)
Withdrawals due to safety	10%	12%	14%
AEs	8%	7%	12%
Lab abnormalities	2%	4%	1%
Withdrawals due to non-safety	17%	7%	9%
Insufficient therapeutic response	6%	2%	1%
Refused treatment	5%	3%	0%
Failure to return	1%	1%	5%
Admin/other	6%	0%	3%
Did not cooperate	0%	0%	0%
Violation of entry criteria	0%	1%	0%
Dose modification	29%	25%	37%
Dose mod due to AE	14%	2%	14%
Dose mod due to lab abnormality	19%	24%	27%
ALT d/o	1%	2%	2%
Neutropenia	14%	9%	11%
Thrombocytopenia	6%	18%	19%
Neotro + Thrombocytopenia	2%	2%	2%
Other	1%	N/A	N/A

Reviewer Comment:

Although numbers of withdrawals were consistent between the groups, the reasons for withdrawal varied. In the standard IFN group, lack of therapeutic response was the main reason for withdrawal. For the PEG-IFN groups, withdrawal was more often related to toxicity, especially thrombocytopenia.

The following tables describes the deaths and serious adverse events that occurred in NV15495. Specific attention has been given to infectious, hemorrhagic and psychiatric events and associated features of the events (laboratory, etc.).

4.1.5.3.2 NV15495 Deaths and Serious Adverse Events

	Stnd IFN	90 PEG	180 PEG
REVIEW OF DISPOSITION OF PATIENTS			
Defining the Safety Population *			
Randomized, n	88	96	87
*** Rand'd+received drug (SAFETY POP), n**	**86**	**96**	**87**
Completed treatment, n	64	78	67

Completed treatment + Completed f/u, n	58	70	65
Follow-up "compliance", %	91	90	97
Deaths / Overall SAEs			
Deaths, n	0	1	3
Deaths related to drug, n	0	0	1 *
Causes of death:			
Psych			
Hemorrhage			Cereb. Hem.*
Infect ion/sepsis			
Other		Hep. fail.	Hep. Failure
			Liver ca
Serious adverse events, n (%)	8 (9)	7 (7)	12 (14)
Psych total (Pts with at least 1 ae), n	0	1	1
Hemorrhage, n	1	1	1
Infection/sepsis, n	1	3	4
Other, n	6	2	6
SERIOUS ADVERSE EVENTS: SELECTED CATEGORIES			
INFECTIONS			
Serious AEs Infections, n	1	3	4
	Cellulitis	Abscess	Local'd inf.
		RTI	Cellulitis
		Pneumonia	Endocarditis
			Wound inf.
Non-serious Infections, n (%)l	34 (40)	34 (35)	37 (43)
Neutrophil Severe Adverse Events*			
Gr 3 neutropenia (0.5 - 0.99 x 10e9/L), %	27	27	48
Gr 4 neutropenia (<0.5 x 10e9/L), %	4	3	1
Normal neutrophil count, %	20	13	4
* Lowest count-Rx + 8 wk. F/u			
Infections & assoc'd Gr 4 neutropenia, n	2 (non-serious)	0	4 (serious)
	Pneumonia		Local'd inf.
	UTI		Cellulitis
			Endocarditis
			Wound inf.
BLEEDING			
Serious AEs Hemorrhage/ platelets, n	1	1	1
	ITP	Variceal hem.	ITP
Non-serious bleeding episodes, %			
Epistaxis	14	11	7
Gingival bleeding	3	6	8

Gr 3 thrombocytopenia (20-49 x 10e9/L), %	6	26	17
Gr 4 thrombocytopenia (<20 x 10e9/L), %	1	0	1
Normal platelet count (>100 x 10e9/L), %	47	32	33
* Lowest count-Rx + 8 wk. F/u			
PSYCHIATRIC			
Psych Serious adverse events, n	0	1	1
		Suicide att.	Suicide att.
Other Psych non-serious Adverse events, n			
Psychiatric total	42	42	44
Psych Gr mod	23	26	26
Psych Gr severe+life-threatening	5	4	1
Depression total (NOS+ mood)	21	22	25
Depression Gr mod	11	16	16
Depression Gr severe+life-threatening	2	2	1

4.1.5.3.3 NV15495 Adverse Events by Body System in > 10% of Patients (Note: Infections, Hemorrhages and Psychiatric AEs Reported Above)

Item				Stnd. IFN (n=86) %	PEG 90 (n=96) %	PEG 180 (n=86) %
All Body Systems						
	Total Pts with at least one AE			99	98	100
	Total number of Aes			836	950	977
General Disorders						
	Total Pts with at least one AE			92	90	90
	Fatigue			60	53	62
	Rigors			45	38	43
	Pyrexia			36	29	38
	Injection site inflammation			14	15	31
	Pain NOS			12	10	10
	Pain in limb			5	11	8
Neurological Disorders				76	77	73
	Headache			55	54	50
	Insomnia			22	19	19
	Dizziness (except vertigo)			16	20	15
	Concentration impairment			12	6	7
Gastrointestinal Disorders						
	Total Pts with at least one AE			76	64	78
	Nausea			34	30	34
	Abdominal Pain Upper			24	20	27
	Diarrhea NOS			19	21	24

	Vomiting NOS			15	13	13
	Abdominal Pain NOS			13	5	8
Musculoskeletal and Bone Disorders						
	Total Pts with at least one AE			69	65	79
	Myalgia			38	36	51
	Arthralgia			26	27	41
	Back pain			19	15	17
Skin and Subcutaneous Tissue Disorder						
	Total Pts with at least one AE			42	47	63
	Alopecia			22	15	17
	Pruritis			8	16	16
	Dermatitis NOS			7	8	17
Respiratory and Thoracic Disorders						
	Total Pts with at least one AE			31	43	41
	Cough			5	10	17
	Epistaxis			14	11	7
Disorders of Metabolism and Nutrition						
	Total Pts with at least one AE			16	22	26
	Appetite decreased			7	15	14
Injury and Poisoning						
	Total Pts with at least one AE			13	13	13
Disorders of the Eye						
	Total Pts with at least one AE			7	13	17
Cardiac Disorders						
	Total Pts with at least one AE			7	15	7

<u>Reviewer Comment</u>:

Four patients who received PEG-IFN died in this study, whereas none of the standard IFN patients died. In the case of one patient, #20561/0369, PEG-IFN was thought by the investigator to be possibly related to the death. Although cerebral hemorrhage was the cause of death of this complicated patient, thrombocytopenia due to PEG-IFN use and pneumonia possibly due to PEG-IFN use were contributing factors. The patient had been an opiate addict, was on methadone at the time of hospitalization, and had what was initially considered a methadone overdose at the time of hospital admission. Opiate levels were not at toxic levels, however, due to the disturbing number of deaths involving PEG-IFN use and opiates, it is not clear what role methadone/PEG-IFN may have played in further complicating the patient's course.

Regarding other serious adverse events, there appeared to be a trend towards more serious infections in the patients who received PEG-IFN. Possibly related to this was the

induction of severe neutropenia in a higher percentage of patients who received PEG-IFN relative to standard IFN. Although thrombocytopenia was also higher in the PEG-IFN treated patients, except for the cerebral hemorrhage death cited above, this did not appear to manifest itself in higher overall numbers of serious bleeding episodes in the PEG-IFN recipients.

Finally, besides the possible role of PEG-IFN in the actions of methadone in the cerebral hemorrhage death cited above, PEG-IFN in study NV15495 did not appear to elicit any more serious psychiatric adverse events than observed in the standard IFN group.

Regarding the other, non-serious adverse events in the study, there did not appear to be a difference in incidence between use of standard versus pegylated interferon alfa-2a.

4.1.6 NV15495 Antibody formation to PEG-IFN

	Stnd. IFN	**90 PEG**	**180 PEG**
Antibody formation	11% (7/65)	4% (3/75)	4%(3/67)

Reviewer Comment: Use of PEG-IFN appears to result in less antibody formation than treatment with standard interferon.

4.1.7 Summary of Efficacy and Safety

Efficacy:

- PEG-IFN was more efficacious than IFN in causing a sustained response as measured by disappearance of HCV and normalization of ALT.
- Results appeared to be consistent amongst the subgroups analyzed by the sponsor, except in the case of race. There is a paucity of data on impact of race on outcome.
- There was evidence that histological improvement occurred in all three treatment groups. Due to incomplete data collection, the treatment effect of PEG-IFN versus control arm cannot be ascertained.
- It was unclear whether PEG-IFN offered an improvement in the Quality of Life of the patients based on the SF36 score and the Fatigue Severity Scale. The detection methods used for this variable may have lacked sensitivity to adequately detect change in the patients and neither instrument has been validated for use in detecting treatment effects in HCV patients. In addition, assessing Quality of Life in an open-label clinical trial setting most likely introduced bias into the results.

Safety:

- PEG-IFN caused many of the same types of adverse events as has been attributed to standard interferon.

- There were no striking differences observed in the percentage of common adverse events in the different patient groups.
- Withdrawals due to adverse events, dose modification and dose modification due to thrombocytopenia were higher in the PEG-IFN group.
- Although dose modification due to neutropenia was the same between the groups, the extent of severe neutropenia was greater in the PEG-IFN treatment group. This may have resulted in a trend towards greater serious infections in this group.
- The extent of thrombocytopenia was also greater in the PEG-IFN group, although it is not clear whether this translated into greater number of bleeding episodes.
- Psychiatric AEs did not appear to differ between groups.

Finally, there is less antibody formation to PEG-IFN compared to the standard formulation evident in Trial NV15495.

4.2 Clinical Trial NV 15496

Title A Phase III Open-Label, Randomized, Multicenter, Parallel Dose Efficacy and Safety Study comparing Pegylated-Interferon α-2a (Ro 25-8310) to a Standard Regimen of Roferon in the Treatment of Patients with Chronic Hepatitis C

4.2.1 Objectives and Design

This Phase 3 clinical trial was to be performed at 30-50 centers in the U.S., Canada, Australia, France and U.K. By the end of the study, the trial had been expanded to 52 centers. The objectives were to confirm that PEG-IFN administered once per week provides superior efficacy and acceptable safety and tolerability as compared to two standard regimens of IFN administered on a tiw basis when administered over 48 weeks to patients with CHC.

The statistical design was that of an open-label, randomized, parallel group study. Treatment groups and numbers of patients were to be as follows:

Roferon n=212, 3 MIU tiw x 48 weeks
PEG n=212, 135 mcg qw x 48 wks
PEG n=212, 180 mcg qw x 48 wks

By the end of the study, 639 patients (versus n=636 planned) had been randomized. Randomization was 1:1:1, with stratification by center.

4.2.2 Inclusion/Exclusion Criteria

Inclusion Criteria: Men and women ≥ 18 years old; serologically proven CHC (anti-HCV antibody test) with compensated liver disease (Child-Pugh Grade A as determined by biopsy within 12 months prior to first dose of study drug. A maximum of 20% of patients were allowed to have cirrhosis or transition to cirrhosis on biopsy); elevated

serum ALT as determined by two abnormal values taken ≥ 14 days apart during the six months before the first dose of study drug with at least one of the determinations obtained ≤ 35 days prior to first dose; quantifiable HCV RNA by ----

Exclusion Criteria: Other forms of liver disease, HIV and hepatocellular carcinoma, pre existing severe depression, cardiac, renal or seizure disorder, retinopathy and prior IFN treatment

4.2.3 Endpoints

Efficacy:

The primary efficacy endpoint was Sustained Response defined as normalized serum ALT concentration and undetectable HCV RNA by ----------at the end of 24 weeks of follow-up.

Secondary efficacy endpoints were: End of treatment virologic and biochemical response; Sustained response (virologic response) at 24 weeks following completion of treatment compared to pre-treatment rates; Histological improvement as measured by comparison of findings pre-treatment and at the end of the 24 weeks of untreated f/u (biopsy within 14 days of EOT). Quality of Life and Fatigue Severity Scale Questionnaire assessment

Safety:

Safety monitoring consisted of assessment of vital signs, labs, adverse events, ECG and chest X-ray. Safety monitoring consisted of assessment of vital signs, labs, adverse events, ECG and chest X-ray. The trial had a Safety Review Board that was to meet every 2-3 months. Safety labs were drawn at various timepoints during treatment and at follow-up and consisted of testing for hematology (CBC with differential, platelets), biochemistry (alkaline phosphatase, AST, ALT, total bilirubin, total protein, albumin, BUN, serum creatinine, chloride, potassium, sodium, calcium, phosphate, uric acid, and cholesterol and triglyceride), urinalysis and thyroid function. Assessment for IFN antibodies was performed at baseline and Week 56.

4.2.4 Statistical Considerations

The statistical analytical plan was based on the goal of demonstrating that the efficacy of either PEG-IFN dose arms was superior to that of the standard IFN control group.

4.2.4.1 Sample Size:

The sample size was predicated on the assumption that the combined Sustained Response Rate in terms of Both virological and biochemical response at the end of untreated follow up of Roferon in non-cirrhotic patients was 20%. 212 patients per treatment arm were required in order to detect a rate of 35% in a PEG treatment arm versus a rate of 20% in

the Roferon arm, with a power of 80%, at a two-sided significance level of 0.025, adjusting for a dropout rate of 15%. Since a total of two pairwise comparisons (PEG 135 vs. Roferon and PEG 180 vs. Roferon) was made, a significance level of 0.025 was to be used in all statistical testing.

4.2.4.2 Analytical group definitions:

- The Intent-to-Treat was all randomized patients.

- The Standard Treatment group had the following criteria for exclusion of data from analysis:

--Patients who never took any study medication
--Patients who took less than 25% of the injections (Patients randomized to the PEG arms and took less than 12 injections [36 for Roferon]will be excluded)
--Patients randomized to the PEG who took less than 4 injections at that dose (<12 for Roferon)
--Patients without compensated liver disease of Child-Pugh Grade A classification
--Patients with baseline HCV RNA < 2000 copies/ml
--Patients without two abnormal ALT levels ≥14 days apart during the six months before the first dose of study medication with at least one of the determinations obtained ≤35 days prior to the first dose
--Patients who received previous treatment with IFN
--Patients who received previous treatment with any other systemic antiviral therapy or investigational drug ≤ 3 months prior to the first dose of study medication, unless permitted by the protocol
--Patients with no post-baseline ALT and HCV RNA assessment

Reviewer Comment:

Note that although analyses using the Standard treatment group were performed, the results did not add appreciably to efficacy information about the product. These results were not requested to be part of the label by the sponsor and they will not be included in this review.

- Primary Efficacy Group – Case Definition of Sustained Responder

For purposes of statistical analyses, the sponsor defined precise case definitions for the primary outcome measure (SVR and SBR at 24 weeks after EOT). Patients without week 68 or 72 data were considered non-responders. Sustained viral responder was defined as having a non-detectable HCV-RNA at both week 68 and week 72. Allowable ranges for collection of these samples were days 464 to 491 for Week 68 and days 492 to 519 for Week 72. Sustained biochemical responder was defined as having a normalized ALT at both week 68 and week 72. Allowable ranges for collection of these samples were days 464 to 491 for Week 68 and days 492 to 519 for Week 72.

In a late amendment to the IND, the sponsor requested [

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Reviewer Comment:

The Agency considered this post-hoc approach to be inherently prone to conscious or unconscious bias and decided that use of the original protocol definition of responder represented the least biased approach in determining responder classification. Appendix 1 includes a more thorough review of this issue.

Secondary Efficacy parameters measured were: Sustained biochemical response rate, induction virological response rate, induction biochemical response rate, end-of-treatment virological response rate, end-of-treatment biochemical response rate, end-of-week 12 virological response rate, end-of-week-12 biochemical response rate, maintenance of virological response after end of treatment, maintenance of biochemical response after end of treatment, absolute and % change from baseline HCV-RNA copies, absolute and % change from baseline ALT levels, duration of virologic response during 48 week treatment period, duration of biochemical response during 48 week treatment period, time to relapse of virologic response, time to relapse of a biochemical response, and histology of liver biopsy and quality of life as measured by the SF-36 scale and the Fatigue Severity Scale (FSS).

- Interim analyses

An interim analysis was planned when all patients had completed 16 weeks of treatment. Since the study was not to be terminated even if significantly superior induction response rates were observed in either PEG arm when compared to the IFN arm, no adjustment of significance level was required at the final comparison of sustained response rates.

- Subgroup analyses

The following groups were segregated and analyzed for the primary efficacy endpoint and key secondary efficacy endpoints: Age, gender, BSA, baseline ALT quotient, baseline HCV RNA titers and HCV genotype.

- Safety analysis

The population for the safety analysis was patients who receive at least one dose of study medication and have at least one post-baseline safety assessment

- Handling of variables:

  Treatment difference – estimated using least square means and corresponding 95% CI

  Time to event variables – used survival analysis techniques including Kaplan-Meier plots, logrank test, Cox proportional hazards regression model stratified by center. Hazard ratios and corresponding 95% CI were given

  Categorical variables – used the Mantel-Haenszel test stratified by center. Odds ratio and corresponding 95% CI were given.

  Changes from baseline variables – used analysis of covariance

  Incidence of adverse events and lab abnormalities were summarized by treatment group

4.2.5 Results

4.2.5.1 NV15496 Disposition of patients / Distribution of baseline variables

	Stnd IFN	135 PEG	180 PEG
DISPOSITION			
Randomized patients	214	215	210
Rand'd, received drug (SAFETY POP)	207	215	208
Completed treatment	144	176	173
Completed Rx,Completed f/u	136	168	162
Follow-up "compliance"	94%	96%	94%
BASELINE CHARACTERISTICS			
ALT, mean	85.1	94	87.7
HCV RNA, mean (10e3 copies/mL)	7907	7502	7974
HAI score, mean	9.5	9.2	9.4
Cirrhosis, %	7	9	5
Transition to cirrhosis, %	10	11	13
Noncirrhosis, %	83	80	82
Genotype 1a, %	43	38	36
Genotype 1b, %	22	27	25
Genotype other, %	35	35	39
Compliance (% receiving 48 weeks)	71	82	84

Reviewer Comment:

Baseline variables generally appear evenly distributed amongst the treatment groups. Compliance with the protocol was also exemplary.

4.2.5.2 Efficacy results

4.2.5.2.1 NV15496 Viral and Biochemical Results

Primary Efficacy Parameter: Sustained Viral Response (SVR) + Sustained Biochemical Response (SBR)(Intent-to-Treat results using the original protocol definition of sustained responder)

Secondary Efficacy Parameters: Sustained Viral Response, Sustained Biochemical Response (Intent-to-Treat results using the original protocol definition of sustained responder)

Group	Total N	SVR + SBR (ITT) n (%)	SVR (ITT) n (%)	SBR (ITT) n (%)
Stnd Roferon	214	19 (9)	19 (9)	28 (13)
135 PEG	215	44 (20)	47 (22)	47 (22)
180 PEG	210	41 (20)	47 (22)	48 (23)

Reviewer Comment:

Pegylated interferon alfa-2a was able to induce a significantly greater sustained viral response than standard interferon. There was no dose-response effect, possibly because both doses were on the plateau of the dose-response curve.

4.2.5.2.2 NV15496 Liver Biopsy Results

	Stnd IFN	135 PEG	180 PEG
All Patients	n=214	n=215	n=210
Number with response	n=66	n=82	n=93
% with improvement (>2 decrease)	31	38	44
Patients With Paired Biopsies	n=147	n=171	n=160
Number with response	n=66	n=82	n=93
Pre-treatment HAI, mean	9.4	9	9.4
Histologic activity index, mean change*	-1.2	-1.1	-2
% with improvement (>2 decrease)	45	48	58

* Total HAI score with Fibrosis

Reviewer's Comment:

Percent of paired biopsies for the standard IFN, and the 90 and 180 mcg PEG-IFN, represent only 69, 80 and 76%, respectively, of the total number of patients in each treatment group. Inferring any conclusions about the effect of treatment on histology in the presence of such a large amount of missing data is problematic. However, the results are consistent with the favorable findings of the relative effects of the treatment on viral load and ALT.

4.2.5.2.3 NV15496 Quality of Life Results

	Stnd. IFN	PEG 135	PEG 180
Quality of Life - SF36 (change in mean from baseline)			
Mental health index (decrease=worse)	-0.8	0.3	-1.8
Standardized mental component	-0.8	-0.3	-0.1
At week 72: Much + somewhat better than 1 yr ago?	25%	40%	39%
Quality of Life - Fatigue Severity Scale			
Total FSS (sum # 1-9, mean change)	1.4	0	-0.5
(week 72 vs. baseline) (increase=feels worse)			

Reviewer Comment:

The results from assessment of quality of life appear inconsistent. One of the three scales indicates a worsening for mental health scores after pegylated interferon use. One of the three scores (global assessment) indicates an improvement, but without a dose-related effect. The fatigue scale indicates no change in fatigue after use of pegylated interferon. Taken together, the results indicate a very mixed response on quality of life as the result

of pegylated interferon use. The scoring systems that were used have not yet been validated as a tool to measure the effect of interferon products on quality of life, so this might have contributed to the equivocal results. Also, use of a subjective endpoint such as Quality of Life in an open label clinical trial such as this might have biased the results and therefore disallow any conclusions.

4.2.5.2.4 NV15496 Analysis of Subgroups

	Stnd IFN	**135 PEG**	**180 PEG**
Viral Sustained Response (all patients)	9%	22%	22%
Viral Sustained Response (subgroups, %)			
Age < 40	14	20	27
Age > 40	6	23	19
Male	8	17	23
Female	10	34	21
Caucasian	9	22	23
Non-caucasian	7	19	21
ALT Quo <3	7	17	20
ALT Quo > 3	12	29	27
RNA < 2 mil	12	30	33
RNA > 2 mil	7	16	13
Geno 1a	2	16	21
Geno 1b	9	9	15
Geno non-1	18	36	30
HAI <10	9	21	19
HAI >10	9	25	29
Histo cirrhosis	0	0	18
Histo non-cirrhosis	10	24	24
Histo transition to cirrhosis	5	22	11

Reviewer Comment:

Note that there was no difference in sustained response rates after subgrouping by race. However, numbers were relatively small and the results are at odds with response rates in NV15495. In general, there is a paucity of data regarding race effects on outcome. Also, the higher response rates for initial RNA <2 million and for genotype non-1 are consistent with previous IFN trials showing superior results in these patient groups.

4.2.5.3 Safety Results

The following table describes the extent and reasons for either withdrawal from study or dose modification in study NV15496.

4.2.5.3.1 NV15496 Withdrawals and Dose Modifications

	Stnd IFN	135 PEG	180 PEG
Withdrawals total	70(33%)	39(18%)	37(18%)
Withdrawals due to safety	10%	10%	10%
Aes	8%	7%	7%
Lab abnormalities	2%	2%	3%
Withdrawals due to non-safety	23%	8%	8%
Insufficient therapeutic response	11%	2%	3%
Refused treatment	7%	3%	3%
Failure to return	2%	2%	1%
Admin/other	2%	1%	1%
Did not cooperate	0%	0%	0%
Violation of entry criteria	1%	0%	0%
Dose modification	15%	21%	33%
Dose mod due to AE	9%	7%	13%
Dose mod due to lab abnormality	7%	15%	23%
ALT d/o	2%	1%	3%
Neutropenia	3%	13%	15%
Thrombocytopenia	1%	3%	7%
Neutro + Thrombocytopenia	0%	1%	1%
Other	1%	0%	1%

Reviewer Comment:

Although numbers of withdrawals were consistent between the groups, the reasons for withdrawal varied. In the standard IFN group, lack of therapeutic response was the main reason for withdrawal. For the PEG-IFN groups, withdrawal was more often related to toxicity, especially thrombocytopenia and neutropenia.

The following table describes the deaths and serious adverse events that occurred in NV15496. Specific attention has been given to infectious, hemorrhagic and psychiatric events and associated features of the events (laboratory, etc.).

4.2.5.3.2 NV15496 Deaths and Serious Adverse Events

	Stnd IFN	135 PEG	180 PEG
REVIEW OF DISPOSITION OF PATIENTS			
Defining the Safety Population *			
Randomized, n	214	215	210
Rand'd, no study drug, n	7		2
*** Rand'd+received drug (SAFETY POP), n**	**207**	**215**	**208**

Completed treatment, n	144	176	173
Completed treatment + Completed f/u, n	136	168	162
Follow-up "compliance", %	94	96	94
Deaths / Overall SAEs			
Deaths, n	1	2	0
Deaths related to drug, n	0	1 *	0
Causes of death:			
Psych		Overdose	
Hemorrhage			
Infection/sepsis			
Other	Air embolism	Pneumonitis*	
Serious adverse events, n (%)	16 (8)	21 (10)	15 (7)
Psych total (Pts with at least 1 ae), n	4	2	1
Hemorrhage, n	2	3	0
Infection/sepsis, n	1	5	8
Other, n	9	11	6
SERIOUS ADVERSE EVENTS: SELECTED CATEGORIES			
INFECTIONS			
Serious AEs Infections, n	2	5	7
	Wound inf'n	Toxic shock	Appendicitis
	Pyrexia	Appendicitis	Corneal inf'n
		Flu	Strep infec'n
		Pneumonia	Gastroent'is
		RTI	Viral labyrinth's
			Viral syndrome
			Endocarditis
Non-serious Infections (total n, %)	66 (32%)	76 (35%)	74 (34%)
Neutrophil Severe Adverse Events*, %			
Gr 3 neutropenia (0.5 - 0.99 x 10e9/L), %	11	33	40
Gr 4 neutropenia (<0.5 x 10e9/L), %	1	3	4
Normal neutrophil count, %	28	10	5
* Lowest count-Rx + 8 wk. F/u			
Infections & assoc'd Gr 4 neutropenia, n	0	3 (non-serious)	2 (non-serious)
		UTI x 2	Oral candid.
		Oral candid.	Tonsilillitis
			1 (serious)
			Strep. Inf.
BLEEDING			
Serious AEs Hemorrhage/ platelets, n	2	3	0
	Rectal hem	Uterine hem.	
	Post-op hem.	Uterine hem.	
		Post-op hem.	

Non-serious bleeding episodes, %			
Epist axis	5	4	4
Gingival bleeding	1	1	3
Platelet Counts			
Gr 3 thrombocytopenia (20-49 x 10e9/L), %	1	3	4
Gr 4 thrombocytopenia (<20 x 10e9/L), %	0	0	0
Normal platelet count (>100 x 10e9/L), %	88	57	60
* Lowest count-Rx + 8 wk. F/u			
Bleeding in Grade 3 thrombocytopenia, n	1	1	2
	Gingival	Epistaxis	Epistaxis
			Bruising
PSYCHIATRIC			
Total events	**207**	**215**	**208**
Psych Serious adverse events (n)	4	2	1
	Depression	Alcoholism	Depression
	Depression	Suicide att.	
	Meth. Withdrl		
	Depression		
Other Psych non-serious Adverse events, n			
Psychiatric total	116	112	112
Psych Gr mod	54	63	56
Psych Gr severe+life-threatening	13	10	11
Depression total (NOS+ mood)	40	45	48
Depression Gr mod	18	22	24
Depression Gr severe+life-threatening	4	4	3

4.2.5.3.3 NV15496 Non-Serious Adverse Events in > 10% of Patients (Note: Infections, Hemorrhages and Psychiatric Reported Above)

Item				Stnd. IFN N=207 %	PEG 135 N=215 %	PEG 180 N=208 %
All Body Systems						
	Total Pts with at least one AE			99	99	100
	Total number of Aes			1896	2061	2161
General Disorders						
	Total Pts with at least one AE			87	89	91
	Fatigue			47	52	53
	Rigors			41	35	37
	Pyrexia			24	27	37
	Injection site inflammation			10	16	16
	Asthenia			14	14	12
	Pain NOS			13	13	13
	Pain in limb			6	10	3

Neurological Disorders			Total with >1	81	73	76
	Headache NOS			58	54	51
	Insomnia			30	19	29
	Dizziness (except vertigo)			13	13	17
	Concentration impairment			9	7	11
Gastrointestinal Disorders						
	Total Pts with at least one AE			58	59	63
	Nausea			33	30	29
	Diarrhea NOS			16	21	27
	Abdominal Pain Upper			14	13	13
Musculoskeletal and Bone Disorders						
	Total Pts with at least one AE			69	66	67
	Myalgia			39	36	34
	Arthralgia			32	30	34
	Back pain			16	18	17
Skin and Subcutaneous Tissue Disorder						
	Total Pts with at least one AE			50	53	60
	Alopecia			27	18	23
	Pruritis			10	13	16
	Dermatitis NOS			8	13	16
Respiratory and Thoracic Disorders						
	Total Pts with at least one AE			28	35	35
	Sore throat NOS			5	12	8
Disorders of Metabolism and Nutrition						
	Total Pts with at least one AE			20	15	19
	Appetite decreased			14	7	13
Injury and Poisoning						
	Total Pts with at least one AE			11	11	12
Disorders of the Eye						
	Total Pts with at least one AE			14	9	19
Disorders of the Reproductive System						
	Total Pts with at least one AE			8	12	13

Reviewer Comment:

One patient receiving PEG-IFN died as a result of an opiate overdose. The disturbing number of such deaths in the PEG-IFN alfa-2a program is summarized and discussed in Appendix 2.

Regarding other serious adverse events, there appeared to be a trend towards more serious infections in the patients who received PEG-IFN. Possibly related to this was the induction of severe neutropenia in a higher percentage of patients who received PEG-IFN relative to standard IFN. Although thrombocytopenia was also slightly higher in the PEG-IFN treated patients, this did not appear to manifest itself in higher overall numbers of serious bleeding episodes in the PEG-IFN recipients.

Finally, besides the possible role of PEG-IFN in the opiate overdose death in this trial, PEG-IFN in study NV15496 did not appear to elicit any more serious psychiatric adverse events than observed in the standard IFN group.

Regarding the other, non-serious adverse events in the study, there did not appear to be a difference in incidence between use of standard versus pegylated interferon alfa-2a.

4.2.6 NV15496 Antibody formation to PEG-IFN

	Stnd. IFN	135 PEG	180 PEG
Antibody formation	16%	4%	1%

Reviewer Comment: Use of PEG-IFN appears to result in less antibody formation than treatment with standard interferon.

4.2.7 Summary of Efficacy and Safety

Efficacy:

- PEG-IFN was more efficacious than IFN in causing a sustained response as measured by disappearance of HCV and normalization of ALT.
- Results appeared to be consistent amongst the subgroups analyzed by the sponsor. There is a paucity of data on impact of race on outcome, however.
- There was evidence that histological improvement occurred in all three treatment groups. Due to incomplete data collection, the treatment effect of PEG-IFN versus control arm cannot be ascertained.
- It was unclear whether PEG-IFN offered an improvement in the quality of life of the patients based on the SF36 score and the Fatigue Severity Scale. The detection methods used for this variable may have lacked sensitivity to adequately detect change in the patients and neither instrument has been validated for use in detecting treatment effects in HCV patients. In addition, assessing Quality of Life in an open-label clinical trial setting most likely introduced bias into the results.

Safety:

- PEG-IFN caused many of the same types of adverse events as has been attributed to standard interferon.
- There were no striking differences observed in the percentage of common adverse events in the different patient groups.
- Dose modification and dose modification due to neutropenia and thrombocytopenia were higher in the PEG-IFN group.
- The extent of severe neutropenia was greater in the PEG-IFN treatment group. This may have resulted in a trend towards greater serious infections in this group.
- The extent of thrombocytopenia was also greater in the PEG-IFN group, although it is not clear whether this translated into greater number of bleeding episodes.
- Psychiatric AEs did not appear to differ between groups. However, one patient receiving PEG-IFN died as the result of an opiate overdose. This death and other deaths related to opiate overdose will be discussed in the Appendix.

Finally, there is less antibody formation to PEG-IFN compared to the standard formulation evident in Trial NV15496.

4.3 Clinical Trial NV15497

Title A Phase III Open-Label, Randomized, Multicenter, Parallel-Dose Efficacy and Safety Study comparing Pegylated-Interferon α-2a (Ro 25-8310) to an Induction Regimen of Roferon in the Treatment of Patients with Chronic Hepatitis C

4.3.1 Objectives and Design

This Phase 3 was to be performed at 25-40 centers outside of the U.S. (U.K., Canada, Germany, Spain, Switzerland, Mexico, Australia, New Zealand and Taiwan). By the end of the study, the trial had been performed at 36 centers. The objectives were to confirm that PEG-IFN administered once per week provided no worse superior efficacy and acceptable safety and tolerability as compared to a standard regimen of IFN administered on a tiw basis when administered over 48 weeks to patients with CHC.

The statistical design was that of an open-label, randomized, parallel group study. Treatment groups and numbers of patients were to be as follows:

Roferon	n=228, 6MIU x 12 weeks, then 3 MIU tiw x 36 weeks
PEG-IFN	n=228, 180 mcg qw x 48 wks

By the end of the study, 531 patients (versus n=456 planned) had been randomized. Randomization was 1:1:1, with stratification by center.

4.3.2 Inclusion/Exclusion Criteria

Inclusion Criteria: Men and women ≥ 18 years old; serologically proven CHC (anti-HCV antibody test) with compensated liver disease (Child-Pugh Grade A as determined by biopsy within 12 months prior to first dose of study drug. A maximum of 20% of patients were allowed to have cirrhosis or transition to cirrhosis on biopsy); elevated serum ALT as determined by two abnormal values taken ≥ 14 days apart during the six months before the first dose of study drug with at least one of the determinations obtained ≤35 days prior to first dose; quantifiable HCV RNA by ----

Exclusion Criteria: Other forms of liver disease, HIV and hepatocellular carcinoma, pre existing severe depression, cardiac, renal or seizure disorder, retinopathy and prior IFN treatment

4.3.3 Endpoints

Efficacy:

The primary efficacy endpoint was Sustained Response defined as normalized serum ALT concentration and undetectable HCV RNA by ----------at the end of 24 weeks of follow-up.

Secondary efficacy endpoints were: End of treatment virologic and biochemical response; Sustained response (virologic response) at 24 weeks following completion of treatment compared to pre-treatment rates; Histological improvement as measured by comparison of findings pre-treatment and at the end of the 24 weeks of untreated follow up (biopsy within 14 days of EOT). Quality of Life and Fatigue Severity Scale Questionnaire assessment

Safety:

Safety monitoring consisted of assessment of vital signs, labs, adverse events, ECG and chest X-ray. Safety labs were drawn at various timepoints during treatment and at follow-up and consisted of testing for hematology (CBC with differential, platelets), biochemistry (alkaline phosphatase, AST, ALT, total bilirubin, total protein, albumin, BUN, serum creatinine, chloride, potassium, sodium, calcium, phosphate, uric acid, and cholesterol and triglyceride), urinalysis and thyroid function. Assessment for IFN antibodies was performed at baseline and Week 56.

4.3.4 Statistical Considerations

The statistical analytical plan was based on the goal of demonstrating that the efficacy of either PEG-IFN dose arms was no worse than that of the standard IFN control group induction regimen.

4.3.4.1 Sample Size

The combined SR rate in terms of both virological response and biochemical response at the end of the untreated follow-up period of Roferon induction regimen, was predicted to be below 25%. The sponsor sought to demonstrate that the efficacy of PEG-IFN was no worse than that of Roferon (one sided equivalence). Also, that PEG was no worse than Roferon by more than 5% in the combined SR rates. Assuming a SR rate of 25% for Roferon and 35% for PEG, a total of 456 patients was required to ensure with 90% confidence probability that the lower limit of the two-sided 95% CI of the difference in the response rate was greater than –0.05. A dropout rate of 15 % was factored into this sample size.

4.3.4.2 Analytical groups

- The Intent-to-Treat was all randomized patients.

- The Standard Treatment group had the following criteria for exclusion of data from analysis:

--Patients who never took any study medication
--Patients who took less than 25% of the injections (Patients randomized to the PEG arms and took less than 12 injections [36 for Roferon]will be excluded)
--Patients randomized to the PEG who took less than 4 injections at that dose (<12 for Roferon)
--Patients without compensated liver disease of Child-Pugh Grade A classification
--Patients with baseline HCV RNA < 2000 copies/ml
--Patients without two abnormal ALT levels ≥14 days apart during the six months before the first dose of study medication with at least one of the determinations obtained ≤35 days prior to the first dose
--Patients who received previous treatment with IFN
--Patients who received previous treatment with any other systemic antiviral therapy or investigational drug ≤ 3 months prior to the first dose of study medication, unless permitted by the protocol
--Patients with no post-baseline ALT and HCV RNA assessment

Reviewer Comment:

Note that although analyses using the Standard treatment group were performed, the results did not add appreciably to efficacy information about the product. These results were not requested to be part of the label by the sponsor and they will not be included in this review.

- Primary Efficacy Group – Case Definition of Sustained Responder

For purposes of statistical analyses, the sponsor defined precise case definitions for the primary outcome measure (SVR and SBR at 24 weeks after EOT). Patients without week 68 or 72 data were considered non-responders. Sustained viral responder was defined as having a non-detectable HCV-RNA at both week 68 and week 72. Allowable ranges for collection of these samples were days 464 to 491 for Week 68 and days 492 to 519 for Week 72. Sustained biochemical responder was defined as having a normalized ALT at both week 68 and week 72. Allowable ranges for collection of these samples were days 464 to 491 for Week 68 and days 492 to 519 for Week 72.

In a late amendment to the IND, the sponsor requested that[

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Reviewer Comment:

The Agency considered this post-hoc approach to be inherently prone to conscious or unconscious bias and decided that use of the original protocol definition of responder represented the least biased approach in determining responder classification. Appendix 1 includes a more thorough review of this issue.

Secondary Efficacy parameters measured were: Sustained biochemical response rate, induction virological response rate, induction biochemical response rate, end-of-treatment virological response rate, end-of-treatment biochemical response rate, end-of-week 12 virological response rate, end-of-week-12 biochemical response rate, maintenance of virological response after end of treatment, maintenance of biochemical response after end of treatment, absolute and % change from baseline HCV-RNA copies, absolute and % change from baseline ALT levels, duration of virologic response during 48 week treatment period, duration of biochemical response during 48 week treatment period, time to relapse of virologic response, time to relapse of a biochemical response, and histology of liver biopsy and quality of life as measured by the SF-36 scale and the Fatigue Severity Scale (FSS).

- Interim analyses

An interim analysis was planned when all patients had completed 16 weeks of treatment. Since the study was not to be terminated even if significantly superior induction response rates were observed in either PEG arm when compared to the IFN arm, no adjustment of significance level was required at the final comparison of sustained response rates.

- Subgroup analyses

The following groups were segregated and analyzed for the primary efficacy endpoint and key secondary efficacy endpoints: Age, gender, BSA, baseline ALT quotient, baseline HCV RNA titers and HCV genotype.

- Safety analysis

The population for the safety analysis was patients who receive at least one dose of study medication and have at least one post-baseline safety assessment

- Handling of variables

Treatment difference – estimated using least square means and corresponding 95% CI

Time to event variables – used survival analysis techniques including Kaplan-Meier plots, logrank test, Cox proportional hazards regression model stratified by center. Hazard ratios and corresponding 95% CI were given

Categorical variables – used the Mantel-Haenszel test stratified by center. Odds ratio and corresponding 95% CI were given.

Changes from baseline variables – used analysis of covariance

Incidence of adverse events and lab abnormalities were summarized by treatment group

4.3.5 Results

4.3.5.1 Disposition of Patients / Distribution of Baseline Variables

	Ind'n IFN	180 PEG
DISPOSITION		
Randomized patients	264	267
Rand'd, received drug (SAFETY POP)	261	264
Completed treatment	161	223
Completed Rx,Completed f/u	154	206
Follow-up "compliance"	96%	92%
BASELINE CHARACTERISTICS		
ALT, mean	94.2	98.7
HCV RNA, mean (10e3 copies/mL)	8159	7427
HAI score, mean	9	8.6
Cirrhosis	10%	4%
Transition to cirrhosis	5%	7%
Noncirrhosis	85%	88%
Genotype 1a	31	30
Genotype 1b	30	33
Genotype other	39	37%
Compliance (% receiving 48 weeks)	63%	84%

Reviewer Comment:

Baseline variables generally appear evenly distributed between the treatment groups. Compliance with the protocol was adequate. ALT mean is slightly elevated and the HCV mean is slightly lower in the 180 mcg group relative to the Induction IFN group. The effect of the primary outcome would be minimal since these two variables have opposite prognostic effects and each would thus likely cancel the other's effect on outcome.

4.3.5.2 Efficacy results

4.3.5.2.1 NV15497 Viral and Biochemical Results

Primary Efficacy Parameter: Sustained Viral Response + Sustained Biochemical Response (Intent-to-Treat results using the original protocol definition of sustained responder)

Secondary Efficacy Parameters: Sustained Viral Response, Sustained Biochemical Response (Intent-to-Treat results using the original protocol definition of sustained responder)

Group	N	SVR + SBR (ITT) n (%)	SVR (ITT) n (%)	SBR (ITT) n (%)
Induction	264	39 (15)	44 (17)	49 (19)
Roferon 180 PEG	267	75 (28)	83 (31)	83 (31)

4.3.5.2.2 NV15497 Liver Biopsy Results

	Ind'n IFN	180 PEG
All Patients	n=264	n=267
Number with response	n=92	n=116
% with improvement (>2 decrease)	35	43
Patients With Paired Biopsies	n=167	n=184
Number with response	n=92	n=116
Pre-treatment HAI, mean	9.2	8.6
Histologic activity index, mean change*	-2	-2.4
% with improvement (>2 decrease)	55	63

* Total HAI score with Fibrosis

Reviewer's Comment:

Percent of paired biopsies for the Induction IFN and the 180 mcg PEG-IFN, represent only 63 and 69%, respectively, of the total number of patients in each treatment group. Inferring any conclusions about the effect of treatment on histology in the presence of such a large amount of missing data is problematic. However, the results are consistent with the favorable findings of the relative effects of the treatment on viral load and ALT.

4.3.5.2.3 NV15497 Quality of Life Results

	Induction IFN	PEG 180
Quality of Life - SF36 (change in mean from baseline)		
Mental health index (decrease=worse)	-1.1	0.7
Standardized mental component	0	0.8
At week 72: Much + somewhat better than 1 yr ago?	34%	44%
Quality of Life - Fatigue Severity Scale		
Total FSS (sum # 1-9, mean change) (week72 vs. baseline) (increase=feels worse)	-1.3	-2.1

Reviewer Comment:

The results from assessment of quality of life appear to show a mild benefit on quality of life as the result of pegylated interferon use. The results are slight though and are at odds with the quality of life results from NV 15495 and NV 15496. The scoring systems that were used have not yet been validated as a tool to measure the effect of interferon products on quality of life, so this might have contributed to the equivocal results seen across all studies. Also, use of a subjective endpoint such as Quality of Life in an open

label clinical trial such as this might have biased the results and therefore disallow any conclusions.

4.3.5.2.4 NV15497 Analysis of Subgroups

	Ind'n IFN	**180 PEG**
Viral Sustained Response (all patients)	17%	31%
Viral Sustained Response (subgroups, %)		
Age < 40	20	40
Age > 40	14	21
Male	15	29
Female	19	35
Caucasian	15	31
Non-caucasian	25	32
ALT Quo <3	12	22
ALT Quo > 3	24	45
RNA < 2 mil	24	42
RNA > 2 mil	12	22
Geno 1a	4	21
Geno 1b	9	22
Geno non-1	34	47
HAI <10	17	30
HAI >10	17	35
Histo cirrhosis	8	25
Histo non-cirrhosis	19	30

Reviewer Comment:

Note that there was no difference in sustained response rates after subgrouping by race. However, numbers were relatively small and the results are at odds with response rates in NV15495. In general, there is a paucity of data regarding race effects on outcome. Also, the higher response rates for initial RNA <2 million and for genotype non-1 are consistent with previous IFN trials showing superior results in these patient groups.

4.3.5.3 Safety Results

The following table describes the extent and reasons for either withdrawal from study or dose modification in study NV15497.

4.3.5.3.1 Withdrawals and Dose Modifications

Withdrawals due to non-safety	29%	10%
Insufficient therapeutic response	20%	5%
Refused treatment	5%	2%
Failure to return	3%	2%
Admin/other	1%	0%
Did not cooperate	0%	0%
Violation of entry criteria	0%	0%
Dose modification	18%	19%
Dose mod due to AE	12%	8%
Dose mod due to lab abnormality	9%	14%
ALT d/o	1%	0%
Neutropenia	7%	11%
Thrombocytopenia	2%	3%
Neutro + Thrombocytopenia	0%	0%
Other	0%	0%

Reviewer Comment:

Numbers of withdrawals were greater in the Induction IFN group. As in trials NV15495 and NV 15496, lack of therapeutic response was a main reason for withdrawal. After accounting for this, the number of withdrawals for other reasons are similar. Slightly more patients withdrew for hematologic toxicity, especially for neutropenia.

The following tables describes the deaths and serious adverse events that occurred in NV15497. Specific attention has been given to infectious, hemorrhagic and psychiatric events and associated features of the events (laboratory, etc.).

4.3.5.3.2 NV 15497 Deaths and Serious Adverse Events

	Induction IFN	**PEG 180**
REVIEW OF DISPOSITION OF PATIENTS		
Defining the Safety Population *		
Randomized, n	264	267
*** Rand'd+received drug (SAFETY POP), n**	**261**	**264**
Completed treatment, n	161	223
Completed treatment + Completed f/u, n	154	206
Follow-up "compliance", %	96	92
Deaths / Overall SAEs		
Deaths, n	0	1
Deaths related to drug, n	0	0

Causes of death:		
Psych		Overdose
Hemorrhage		
Infection/sepsis		
Other		
Serious adverse events, n (%)	14 (5)	22 (8)
Psych total (Pts with at least 1 ae), n	3	6
Hemorrhage, n	1	0
Infection/sepsis, n	3	6
Other, n	7	10
SERIOUS ADVERSE EVENTS: SELECTED CATEGORIES		
INFECTIONS		
Serious AEs Infections, n	3	5
	Pyrexia	Pyrexia
	Tuberculosis	Colitis
	Appendicitis	UTI
		Pyeloneph'is
		Diverticulitis
Non-serious Infections, n (%)	75 (29)	97 (37)
Neutrophil Severe Adverse Events*		
Gr 3 neutropenia (0.5 - 0.99 x 10e9/L), %	21	40
Gr 4 neutropenia (<0.5 x 10e9/L), %	2	5
Normal neutrophil count, %	14	5
* Lowest count-Rx + 8 wk. F/u		
Infections & assoc'd Gr 4 neutropenia, n	0	1(non-serious)
		UTI
		3 (serious)
		Pyrexia
		UTI
		Carbuncle
BLEEDING		
Serious AEs Hemorrhage/ platelets, n	1	0
	Uterine hem.	
Non-serious bleeding episodes		
Epistaxis, %	3	2
Gingival bleeding, %	2	3
Gr 3 thrombocytopenia (20-49 x 10e9/L), %	2	2
Gr 4 thrombocytopenia (<20 x 10e9/L), %	0	0
Normal platelet count (>100 x 10e9/L), %	84	59
* Lowest count-Rx + 8 wk. F/u		
Bleeding in Grade 3 thrombocytopenia, n	3	2

	Gingival	Gingival
	Epistaxis	Epistaxis
	Bruising	
PSYCHIATRIC		
Total adverse events	**261**	**264**
Psych Serious adverse events, n	3	6
	Psychosis	Depression
	Depression	Hysteria
	Suicide att.	Depression
		Psychosis
		Depression
		Depression
Other Psych non-serious Adverse events, n		
Psychiatric total	124	107
Psych Gr mod	74	59
Psych Gr severe+life-threatening	31	15
Depression total (NOS+ mood)	76	46
Depression Gr mod	38	23
Depression Gr severe+life-threatening	11	7

4.3.5.3.3 Non-Serious Adverse Events in > 10% of Patients (Note: Infections, Hemorrhages and Psychiatric AEs Reported Above)

Item				IFN 6/3 N=261 %	PEG 180 N=265 %
All Body Systems					
	Total Pts with at least one AE			100	97
	Total number of Aes			2571	2482
General Disorders					
	Total Pts with at least one AE			94	87
	Fatigue			65	60
	Pyrexia			52	37
	Rigors			43	27
	Injection site inflammation			7	10
Neurological Disorders				81	74
	Headache NOS			66	60
	Insomnia			24	18
	Dizziness (except vertigo)			16	23
	Concentration impairment			11	5
Gastrointestinal Disorders					
	Total Pts with at least one AE			62	57
	Nausea			35	21

	Diarrhea NOS			20	19
	Abdominal Pain Upper			14	13
	Vomiting NOS			12	6
	Abdominal Pain NOS			10	8
Musculoskeletal and Bone Disorders					
	Total Pts with at least one AE			75	67
	Myalgia			43	42
	Arthralgia			37	31
	Back pain			17	17
Skin and Subcutaneous Tissue Disorder					
	Total Pts with at least one AE			61	55
	Alopecia			37	27
	Pruritis			12	18
Respiratory and Thoracic Disorders					
	Total Pts with at least one AE			32	38
	Cough			10	9
	Nasopharyngitis			8	11
Disorders of Metabolism and Nutrition					
	Total Pts with at least one AE			28	27
	Appetite decreased			21	20
Disorders of the Eye					
	Total Pts with at least one AE			17	19

Reviewer Comment:

One patient receiving PEG-IFN died as a result of an opiate overdose. The disturbing number of such deaths in the PEG-IFN alfa-2a program is summarized and discussed in Appendix 2.

Regarding other serious adverse events, there appeared to be a trend towards more serious infections in the patients who received PEG-IFN. Possibly related to this was the induction of severe neutropenia in a higher percentage of patients who received PEG-IFN relative to standard IFN. Unlike the other two studies under review, there was no difference in the degree of thrombocytopenia between the groups.

Finally, in addition to the possible role of PEG-IFN in the opiate overdose death in this trial, PEG-IFN in study NV15497 appeared to elicit a slightly higher number of serious psychiatric adverse events (n=6) than observed in the standard IFN group (n=3).

Regarding the other, non-serious adverse events in the study, there did not appear to be a difference in incidence between use of standard versus pegylated interferon alfa-2a.

4.3.6 NV 15497 Antibody formation to PEG-IFN

	Induction IFN	PEG 180
Antibody formation	17%	2%

Reviewer Comment: Use of PEG-IFN appears to result in less antibody formation than treatment with standard interferon.

4.3.7 Summary of Efficacy and Safety

Efficacy:

- PEG-IFN was more efficacious than IFN in causing a sustained response as measured by disappearance of HCV and normalization of ALT.
- Results appeared to be consistent amongst the subgroups analyzed by the sponsor. There is a paucity of data on impact of race on outcome, however.
- There was evidence that histological improvement occurred in both treatment groups. Due to incomplete data collection, the treatment effect of PEG-IFN versus control arm cannot be ascertained.
- In NV15497, there appeared to be a mild improvement in quality of life as the result of use of pegylated interferon. The result was slight, however, and at odds with the results of the other two studies outlined in this review. The detection methods used for this variable may have lacked sensitivity to adequately detect change in the patients, since none of the instrument used have been validated for use in detecting interferon effects in HCV patients. In addition, assessing Quality of Life in an open-label clinical trial setting most likely introduced bias into the results.

Safety:

- PEG-IFN caused many of the same types of adverse events as has been attributed to standard interferon.
- There were no striking differences observed in the percentage of common adverse events in the different patient groups, although the proportion of adverse events reported as severe was slightly higher in the induction interferon group versus PEG-IFN 180 (9 vs.6%).
- Dose modification due to neutropenia and thrombocytopenia were higher in the PEG-IFN group.
- The extent of severe neutropenia was greater in the PEG-IFN treatment group. This may have resulted in a trend towards greater serious infections in this group.
- The extent of thrombocytopenia was not greater in the PEG-IFN group.
- Psychiatric AEs did not appear to differ between groups. However, one patient receiving PEG-IFN died as the result of an opiate overdose. This death and other deaths related to opiate overdose will be discussed in the Appendix.

Finally, there is less antibody formation to PEG-IFN compared to the standard formulation evident in Trial NV15497.

5.0 INTEGRATED SUMMARY OF EFFICACY

Prior to submission of the BLA for PEG-IFN, the sponsor and FDA agreed upon the following structure for the Integrated Summary of Efficacy (ISE):

The ISE consisted of the efficacy data from the three pivotal trials described above. Results of the one Phase 2/3 study (NV15495, n=271) and the two Phase 3 studies (NV15496, n=639 and NV15497, n=531) were presented by the sponsor side by side as well as pooled (NV15496 and NV15497 were pooled). The sponsor also chose to pool only the patients from all three studies who had a histological diagnosis of cirrhosis or transition to cirrhosis (n=456) to present results only on that subgroup. Because the efficacy results of this subgroup were essentially identical to the results of the NV15495 study, this review will only address the pooled non-cirrhotic group. The primary efficacy outcome measure will be addressed, as well as any secondary and subgroup analyses that are relevant to the proposed label for the product.

Efficacy parameters

Because the composition of the treatment groups were relatively uniform, and the endpoints chosen were identical between trials, it was considered appropriate to allow data to be merged for the integrated analyses. Please see the Statistical Review regarding any statistical issues in the merging of the data.

Primary Efficacy Endpoint

The primary efficacy endpoint was Sustained Response defined as normalized serum ALT concentration and undetectable HCV RNA by ----------at the end of 24 weeks of follow-up.

Label-related Secondary efficacy endpoints were:

- Sustained response to treatment (virologic and biochemical response)
- End of treatment virologic and biochemical response
- Histological improvement as measured by comparison of findings pre-treatment and at the end of the 24 weeks of untreated follow up (biopsy within 14 days of EOT).
- Quality of Life and Fatigue Severity Scale Questionnaire assessment

Results:

	POOLED DATA FROM NV15496/NV15497			
Endpoint				
	IFN (Stnd. or Induction)	**135 PEG**	**180 PEG**	**p Value**
Combined Sustained Virologic	60 (13%)	50 (23%)	119 (25%)	0.001
Response (SVR) and Sustained				
Biochemical Response (SBR)				
SVR	65 (14%)	54 (25%)	135 (28%)	0.001
SBR	80 (17%)	54 (25%)	137 (29%)	0.001
End of Treatment (Week 48) VR	107 (22%)	96 (45%)	255 (53%)	0.001
End of Treatment (Week 48) BR	129 (27%)	57 (27%)	165 (35%)	0.011 *
* Note that this was the only parameter in the clinical studies that did not attain statistical significance				

Reviewer Comment: The results from the merged data are similar to the findings in the individual clinical trials. PEG-IFN appears to be more efficacious than standard IFN. The dose-response effect appears to already be at the plateau at the 135 mcg q week dose.

6.0 INTEGRATED SUMMARY OF SAFETY

Prior to submission of the BLA for PEG-IFN, the sponsor and FDA agreed upon the following structure for the ISS:

The primary safety analysis population is pooled from the four monotherapy studies in CHC and includes those patients (cirrhotic and noncirrhotic) assigned to PEG-IFN at the 135 and 180 mcg dose and is compared to either the standard or the induction regimen of IFN. Data from patients randomized to treatment with one of the remaining three doses of PEG-IFN evaluated in the four monotherapy CHC studies (i.e., 45, 90 and 270 mcg) were not included in the primary safety analyses because (1) the 45 mcg dose was not considered effective for the general population with CHC, (2) the 90 mcg dose was not well studies in the general CHC population, and (3) the 270 mcg dose of PEG-IFN exceeds the maximum recommended dose in the treatment of patients with CHC.

For labeling purposes, the following integrated results were submitted for integration into the product safety section. The AEs for the two control regimens are separated due to their different safety profiles. The 135 mcg dose has the same spectrum of AEs as the 180 mcg dose, so the 135 mcg data is not included to simplify the table:

Adverse Reactions Occurring in ³10% of Patients in Hepatitis C Clinical Trials

	IFN 3 MIU N = 323		IFN 6/3 MIU N = 261		PEG-IFN 180 mcg N = 604	
	N	(%)	N	(%)	N	(%)
General						
Fatigue	147	(46)	152	(58)	309	(51)
Rigors	134	(41)	112	(43)	202	(33)
Pyrexia	94	(29)	141	(54)	212	(35)
Injection site reaction	71	(22)	40	(15)	133	(22)
Pain	46	(14)	27	(10)	73	(12)
Gastrointestinal						
Nausea	101	(31)	80	(31)	148	(25)
Diarrhea	44	(14)	48	(18)	103	(17)
Abdominal pain	50	(15)	35	(13)	92	(15)
Nausea and vomiting	19	(6)	25	(10)	33	(5)
Metabolic and Nutritional						
Anorexia	37	(11)	61	(23)	104	(17)
Musculoskeletal, Connective Tissue and Bone						
Myalgia	115	(36)	108	(41)	218	(36)
Arthralgia	87	(27)	82	(31)	162	(27)
Back pain	31	(10)	27	(10)	51	(8)
Neurological						
Headache	174	(54)	165	(63)	326	(54)
Insomnia	78	(24)	57	(22)	119	(20)
Dizziness (excluding vertigo)	33	(10)	39	(15)	94	(16)
Concentration impairment	31	(10)	26	(10)	48	(8)
Psychiatric						
Depression	51	(16)	57	(22)	113	(19)
Irritability	67	(21)	29	(11)	87	(14)
Skin and Subcutaneous Tissue						
Alopecia	78	(24)	92	(35)	141	(23)
Pruritus	20	(6)	24	(9)	68	(11)

Adverse reactions reported in =2%, but <10% on PEGASYS were: asthenia, lethargy, chest pain not otherwise specified, influenza-like illness, malaise, hot flushes not otherwise specified, shivering, memory impairment, paresthesia, taste disturbance, weakness, hypoesthesia, tremor not otherwise specified, muscle cramps, neck pain, dermatitis, sweating increased, rash, dry skin, night sweats, photosensitivity reaction not otherwise specified, dry mouth, gingival bleeding, mouth ulceration, anxiety, mood alteration, libido decreased, nervousness, aggression, weight decrease, cough, dyspnea, sore throat,

nasopharyngitis, vision blurred, eye inflammation, hypothyroidism, palpitations, and flushing.

6.1 Supporting Safety Data from Other Clinical Trials

In addition to the safety data from the Phase 2 and 3 pivotal trials for PEG-IFN, the sponsor also provided data from the early Phase 2 PEG-IFN studies and emerging data from their PEG-IFN+Ribavirin clinical program. Safety information as of July, 2000 relevant to the review of PEG-IFN are presented below:

	Other PEG-IFN Trials				
Item	**Phase 2 NV15489**				
	Stnd IFN	PEG 45	PEG 90	PEG 180	PEG 270
	n=30	n=20	n=20	N=45	N=40
SAFETY					
Deaths	0	1	0	0	0
Psych		Overdose			
Infections/sepsis					
Serious Adverse Events -TOTAL	4	0	2	9	5
Psych	0	0	0	1	0
				Mania	
Infection/sepsis	2	0	0	1	0
	Gastroent			Pyeloneph	
	Gastroent				
Other	2	0	2	7	5

	PEG-IFN + Ribavirin Program (as of July 2000)		
Item	**Phase 3 NV15801**		**Phase 3 NV15942**
	Rebetron	PEG 180	PEG (180 mcg) +
		& Riba	Ribavirin (2 regimens)
SAFETY			
Deaths	0	0	2
Psych			Overdose (opiates)
Infections/sepsis			Local infection >> Sepsis

Serious Adverse Events -TOTAL			
Psych			Suicidal ideation (severe)
Infection/sepsis		UTI hosp'n	S. aureus sepsis
			Sarcoidosis hosp'n
			Osteomyelitis
Other			Atrial fib hosp'n

7.0 OVERALL REVIEWER SUMMARY OF PRODUCT

7.1 Efficacy

- In each of the three pivotal trials of PEG-IFN, evidence was provided that PEG-IFN was more efficacious than IFN in causing a sustained response as measured by disappearance of HCV and normalization of ALT.
- Results appeared to be consistent amongst the subgroups analyzed by the sponsor, with the exception of race. There appears to be a paucity of data on impact of race on outcome. Low initial viral load and non-type 1 genotype continue to be favorable prognostic indicators.
- There was evidence that histological improvement occurred in all IFN treated patients. The suboptimal (approximately 60%) capture of paired biopsy data resulted in the inability to determine differences between PEG-IFN and IFN effect on the outcome measure.
- It was unclear whether PEG-IFN offered an improvement in the quality of life of the patients based on the SF36 score and the Fatigue Severity Scale. The detection methods used for this variable may have lacked sensitivity to adequately detect change in the patients and neither instrument has been validated for use in detecting treatment effects in HCV patients. Assessing a subjective endpoint in an open label trial setting likely introduced bias into the results.
- It appears that there is less antibody formation to PEG-IFN compared to the standard formulation.

7.2 Safety

- PEG-IFN alfa-2a caused many of the same types of adverse events as has been attributed to standard interferon.
- There were no striking differences observed in the percentage of common adverse events in the different patient groups.

- Withdrawals due to adverse events and dose modifications were generally greater in the PEG-IFN treatment arms. This appeared to mostly be due to the toxic effect of PEG-IFN on bone marrow constituents.
- The effect on neutrophils specifically may have resulted in a trend towards greater serious infections as a result of PEG-IFN treatment.
- The extent of thrombocytopenia was also generally greater in the PEG-IFN groups, although it is not clear whether this translated into greater number of bleeding episodes.
- Psychiatric AEs did not appear to differ between groups, although as discussed in Appendix 2, there was a disturbing number of deaths due to or related to overdose of opioid agents.

7.3 Antibody Production

Use of pegylated interferon alfa-2a resulted in a lower incidence of antibody to interferon compared to treatment with standard interferon alfa-2a.

8.0 RECOMMENDED PHASE IV COMMITMENTS

- The sponsor should perform a drug interaction study to assess the interaction between an opiate compound (e.g., methadone) and PEG-IFN.

- [

]

- The sponsor should perform studies adequate to ascertain the effect of race on treatment outcome.

9.0 RECOMMENDED REGULATORY ACTION

A Complete Response letter should be sent to the Sponsor. The Clinical comments are as follows:

1) Your submission includes results from analyses by a review board that shows the response rate for patients receiving pegylated interferon to be much higher than was demonstrated following analyses using protocol defined response criteria. Please be aware that these data and analyses are of secondary importance to those originally proposed and discussed with the agency.
2) Please provide data supporting the SF36 as a validated tool for measuring Quality of Life in patients with chronic hepatitis C.

3) Please provide data supporting the Fatigue Severity Scale as a validated tool for measuring Quality of Life in patients with chronic hepatitis C.
4) Please provide data supporting the SF 36 as a validated tool for measuring the effect of interferon products on Quality of Life in patients with chronic hepatitis C.
5) Please provide data supporting the fatigue Severity Scale as a validated tool for measuring the effect of interferon products on Quality of Life in patients with chronic hepatitis C.
6) Although pegylated interferons are associated with a higher number and frequency of certain adverse events including serious infections, thrombocytopenia and neutropenia, you state that treatment with the product was associated with better quality of life and less fatigue than that observed in the control groups. Please explain.
7) Definitive conclusions about the effect of pegylated interferon alfa-2a on liver histology cannot be made due to the large amount of missing data on this parameter. Please supply any additional information on liver histology not supplied to the BLA.
8) Please provide additional relevant data explaining a significant number of deaths due to or involving opiate overdose in PEG-IFN treated patients versus the IFN control groups. Include in your response physician hospital summaries, autopsy findings, other physician generated summary documents characterizing the clinical findings and course of the following patients:

- NV15489, #18265/0106
- NV15496, #20881/1361
- NV15495, #20561/0369
- NV15497, #20983/2689
- NV15942, #2335 (site number not provided in SAE report)

Also, please provide copies of source data from toxicology testing for all of the listed patients.

9) Some former opiate addicts who had been in recovery for several years appeared to quickly resume their addictive behavior after receiving pegylated interferon-alfa 2a. Specifically patient 106 had been without opiates for 8 years and died of an opiate overdose within 138 days of starting pegylated interferon-alfa 2a. Also, patient 2335 had been without opiates for 10 years and died of an opiate overdose within 31 days of starting pegylated interferon-alfa 2a. Please comment.
10) There appears to be a significant number of serious infections that occurred in patients who received pegylated interferon alfa-2a. For example, in trial NV15496 there were 2 serious adverse events due to infections in the standard interferon group and a total of 12 serious adverse events due to infections in the patients who received pegylated interferon-alfa 2a. Also, in trial NV15497, there were three serious infections and one non-serious infection associated with Grade 4 neutropenia and receipt of pegylated interferon alfa-2a. This trend has continued with the ongoing NV15942 study, wherein there has been one death due to sepsis, and three serious adverse events due to infection (*S. aureus* sepsis, sarcoidosis and osteomyelitis). Please comment on the association between pegylated interferon-alfa 2a and serious infections.
11) Regarding Trial NV15495, patient 19153/0262, thrombocytopenia secondary to pegylated interferon alfa-2a appeared to be associated with the onset of events

resulting in the death of this patient. Please provide additional clinical data (physician hospital summaries, autopsy findings, other physician generated summary documents) characterizing the clinical findings and course of this patient.

12) Regarding Trial NV15495, patient 20561/0369, please provide additional clinical data (physician hospital summaries, autopsy findings, other physician generated summary documents) characterizing the clinical findings and course of this patient.
13) Regarding Trial NV15495, patient 21713/0642, please provide additional clinical data (physician hospital summaries, other physician generated summary documents) characterizing the clinical findings and course for this patient who developed and was hospitalized for the treatment of pneumonia.
14) Regarding Trial NV15495, patient 19155/0321, please provide additional clinical data (physician hospital summaries, other physician generated summary documents) characterizing the clinical findings and course for this patient who developed and was hospitalized for the treatment of idiopathic thrombocytopenia purpura.
15) Regarding Trial NV15496, patient 20862/0904, please provide additional clinical data (physician hospital summaries, other physician generated summary documents) characterizing the clinical findings and course for this patient. Also, please provide copies of the source data from the hematologic testing that occurred during the patient's hospitalization for abdominal pain, rigors and pyrexia.
16) Regarding Trial NV15496, patient 20860/0075, please provide additional clinical data (physician hospital summaries, other physician generated summary documents characterizing the clinical findings and course for this patient who developed and was hospitalized for the treatment of toxic shock syndrome.
17) Regarding Trial NV15496, patient20993/1752, please provide additional clinical data (physician hospital summaries, other physician generated summary documents) characterizing the clinical findings and course for this patient who developed and was hospitalized for the treatment of neutropenia.
18) Regarding Trial NV15497, patient 20983/2689, please provide additional clinical data (physician hospital summaries, autopsy findings, other physician generated summary documents) related to the death of this patient.
19) Regarding Trial NV15497, patient20986/2431, please provide additional clinical data (physician hospital summaries, other physician generated summary documents) characterizing the clinical findings and course for this patient. Please include results of all hematological testing that was performed during his admission.
20) Regarding Trial NV15497, patient 20979/2649, please provide additional clinical data (physician hospital summaries, other physician generated summary documents) characterizing the clinical findings and course for this patient who developed and was hospitalized for the treatment of encephalitis.
21) Regarding Trial NV15497, patient 21208/2934, please provide additional clinical data (physician hospital summaries, other physician generated summary documents) characterizing the clinical findings and course for this patient who developed and was hospitalized for the treatment of autoimmune hepatitis.
22) Regarding Trial NV15942, patient --641, please provide additional clinical data (physician hospital summaries, autopsy findings, other physician generated summary documents) related to the death of this patient.

23) Regarding Trial NV15942, patient ---2335, please provide additional clinical data (physician hospital summaries, autopsy findings, other physician generated summary documents) related to the death of this patient.

In addition the sponsor should be notified that, should the product be approved, the following post-marketing commitment will be required. Specific comments for this letter are:

1) Please provide a plan to evaluate the pharmacokinetics and pharmacodynamics of methadone patients who received Pegylated interferon alfa-2a.

2) [ ]

3) The data submitted in your license application do not adequately address the safety and efficacy of pegylated interferon alfa-2a in various ethnic groups, as over 90 percent of study participants were Caucasians. In the three pivotal studies, the response rates for non-Caucasians was unclear and did not all for meaningful conclusions to be drawn whether ethnic subgroups respond differently than Caucasians after accounting for other prognostic factors.

Please describe your plans to address the above issues in sufficient detail to permit our evaluation of the adequacy of the proposals. We request that your response include:

- A detailed protocol or, at a minimum, a detailed outline describing all design features of the study including sample size and justification, eligibility criteria with rationale, dosing regimens and duration, clinical assessments to be performed and their timing, and endpoints to be analyzed

- A proposed timeline for conducting the study, including all major milestones for the study, e.g., finalization of the protocol, initiation of enrollment, completion of enrollment, completion of all patient dosing and follow up, and completion of the data analysis, and submission of the final study report and applicable revised labeling to the FDA.

10.0 APPENDICES

10.1 Appendix 1

Analysis of post-hoc ----------

As a result of the post-hoc ----------

BLA 99-2672 PEGASYS Efficacy

Phase 2/3 Groups	N	Primary Efficacy Endpoint Viral+Bio Sustained Response Original	Amended	Abs. inc, % inc.* (based on total n)
Stnd Roferon	88	4 (5%)	7 (8%)	3, +3%
90 PEG	96	11 (11%)	14 (15%)	3, +4%
180 PEG	87	17 (20%)	26 (30%)	9, +10%

* Original protocol compared to amended protocol

Phase 3 Groups	Total N	Primary Efficacy Endpoint Viral+Bio Sustained Response Original	Amended	Abs. inc, % inc.* (based on total n)
Stnd Roferon	214	21 (10%)	23 (11%)	2, +1%
135 PEG	215	50 (23%)	59 (27%)	9, +4%
180 PEG	210	42 (20%)	55 (26%)	13,+6%

* Original protocol compared to amended protocol

Phase 3 Groups	N	Primary Efficacy Endpoint Viral+Bio Sustained Response Original	Amended	Abs. inc, % inc.* (based on total n)
Induction Roferon	264	39 (15%)	46 (17%)	7, +2%
180 PEG	267	77 (29%)	101 (38%)	24, +9%

* Original protocol compared to amended protocol

BLA 99-2672 PEGASYS Efficacy

BLA 99-2672 PEGASYS Efficacy

Phase 2/3 Groups	N	Secondary Efficacy Endpoint Viral Sustained Response Original	Amended	Abs. inc, % inc.* (based on total n)
Stnd Roferon	88	5 (6%)	7 (8%)	2, +2%
90 PEG	96	12 (13%)	14 (15%)	2, +2%
180 PEG	87	25 (29%)	26 (30%)	1, +1%

* Original protocol compared to amended protocol

Phase 3 Groups	Total N	Secondary Efficacy Endpoint Viral Sustained Response Original	Amended	Abs. inc, % inc.*

				(based on total n)
Stnd Roferon	214	21 (10%)	23 (11%)	2, +1%
135 PEG	215	54 (25%)	61 (28%)	7, +3%
180 PEG	210	48 (23%)	58 (28%)	10, +5%

* Original protocol compared to amended protocol

Phase 3 Groups	N	Secondary Efficacy Endpoint Viral Sustained Response Original	Amended	Abs. inc, % inc.* (based on total n)
Induction Roferon	264	44 (17%)	50 (19%)	6, +2%
180 PEG	267	87 (33%)	103 (39%)	16, +6%

* Original protocol compared to amended protocol

Regardless of study or treatment arm within studies, the review board consistently assigned a higher response rate to the PEG treatment arm the standard IFN control arm.

The differences are not explained by a higher dropout rate in the standard IFN arms.

[

]

[

] Therefore for issues of product labeling, it is recommended to use the results obtained from the original protocol definition of responder (within the intent-to-treat group) as the best and least biased reflection of the efficacy of PEG-IFN in patients with chronic hepatitis C infection.

10.2 Appendix 2

Analysis of deaths due to or involved with opiate overdose

An issue that evolved during the review of the deaths that occurred during development of Pegylated Interferon alfa-2a was the number of deaths due to or involved with an overdose of drugs in the opiate class. A tabulation of details surrounding the deaths follows:

Pt. No.	Age	PEG Dose	Days of treatment	Day of death	Coroner Opinion	Opiate Level	Confounding factors
106	40	45	106	138	Accidental opiate OD	Not provided	Previous h/o/ heroin abuse, but OK for 8 yrs., History of depression, started on anti-dep. day 48, stopped by psychiatrist day 53
Comment: Depression may have contributed to decision to re-start opiates. Assuming lethal level of opiates, PEG/opiate interaction difficult to discern.							
1361	32	135	At least 56	88	Accidental OD	Therapeutic Level	H/o drug abuse. Drugs at autopsy: (diazepam,codeine,methadone,alcohol) H/o suicidal behavior. Recent extreme behavior. Drug levels taken 24 hours after death.
Comment: Therapeutic levels of opiates raise suspicion of PEG/opiate potentiation, but levels taken late is confounding.							
369	45	180	57	81	Massive cerebral Hemorrhage	Below Toxic level	Previous h/o alcohol, amphetamine and opiate abuse. Day 65 suspected methadone OD with severe resp. depression. Thrombocytopenia caused by PEG. Associated coagulopathy that may have contributed to bleed.
Comment: Methadone only minimally contributory in death. However, admission respiratory depression with sub-toxic levels of Methadone may point to PEG/opiate potentiation. Underlying admission LRTI confounds this, however.							
2689	44	180	337	347	Combined heroin and Alcohol Intoxication	Fatal levels of morphine	Previous h/o/ injection drug abuse.
Comment: Temporally related to PEG, but lethal levels of morphine make discerning PEG/opiate interaction difficult.							
2335	32	180	28 (approx.)	31	Accidental opiate OD	Possible Lethal level	Previous i.v. abuser, but OK for 10 yrs. No h/o/depression, no associated life changes around time of death
Comment: Suspicious for PEG/opiate interaction, especially with uncertain opiate levels.							

Although the total number of deaths due to or related to opiate overdose are few, it is striking that no patient deaths in the standard IFN were due to this cause. However, the trends for a role of PEG-IFN in these deaths are confounded by other events occurring in the patients' lives at the time of death and the other illicit medications that the patients were generally consuming with opiates. Despite this, though, in the case of a least one of the deaths (patient 2335 above), there did not appear to be related life events that resulted in the resumption of previous opiate use except for the receipt of PEG-IFN.

A potential hypothesis for the role of PEG-IFN in resumption of addictive behavior or pharmacological interaction between PEG-IFN and consumed opiates relates to the involvement of endogenous interferon in CNS pathways mediated by endogenous opioids. It appears that interferon binds to the opiate receptor and that it can interact centrally with the actions of both endogenous and exogenous opioids. In addition, interferon may alter the metabolism of opiate compounds through actions on hepatic enzymes.

Although this hypothesis would implicate standard IFN in the same neurological processes, it could be argued that the enhanced potency of PEG-IFN on other parameters (both efficacy and safety) might also enhance its effect as a mediator of the endogenous opioid CNS pathways. Without further evidence of PEG-IFN – opiate interaction, however, this phenomenon should otherwise be monitored during the post-marketing phase of the product cycle to see whether exposure of PEG-IFN to larger populations poses a definitive public health risk. It is also recommended that the sponsor perform a drug interaction study to explore the possible relationship between PEG-IFN and opiate products.

Submitted by:

_____ _____

Mark O. Thornton, M.D., M.P.H., Ph.D. Date
Medical Officer
FDA/CBER/OTRR/DCTDA